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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,519	09/09/2003	David Sidransky	JHU1300-6	6054

7590 01/28/2008

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ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
01/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,519	SIDRANSKY ET AL.	
	Examiner	Art Unit	
	Katherine Salmon	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-24* is/are pending in the application.

4a) Of the above claim(s) *20-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/20/2007 has been entered.

2. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 20-24 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 12-19 have been elected without traverse in the reply filed 6/15/2006.

Withdrawn Objections

3. The objection to Claim 13 made is section 8 of the previous office action is moot based on amendments to the claims.

Withdrawn Rejections

4. The rejection of the claims under 35 USC 112/second paragraph, second paragraph made in section 9 of the previous office action is moot in view of the amendments to the claims.

5. The rejection of the claims under 35 USC 112/New Matter made in section 9 of the previous office action is moot in view of the amendments to the claims.

Priority

6. The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 08/439962, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Application No. 08/439962 does not support the detection of hypermethylation of CpG island in the first exon. The filing date therefore will be based on application 08/497535 and is 06/30/1995.

Oath/Declaration

7. The oath is objected to because the oath discloses that the instant application is a continuation of application 08/497535. The oath should be amended to indicate that the instant application is a CIP of application 08/497535.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 12-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12-19 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: steps for detecting hypermethylation.

Claims 12-19 are unclear over the steps of "detecting a first amplification product comprising exon 2 of the p16 gene in the absence of identifying a second amplification product comprising exon 1 of the p16 gene, wherein hypermethylation of a 5' CpG island in the fist exon of the p16 gene is associated with the presence of the truncated product". The detection of a first amplification product comprising exon 2 would also comprise exon 1.

Claims 13 and 16 are unclear over the step of "contacting the sample with a demethylating agent and wherein the presence of the demethylating agent, the second amplification product is detectable when methylation of the 5' CpG island in the first exon results in a truncated p16 product lacking exon 1". This step seems to contradict the steps of Claim 12. Claim 13 required a demethylation step in the presence of the sample and primers in step A, whereas claim 12 is drawn to detection of methylation. Further Claim 13 is drawn to detection of methylation whereas Claim 12 is drawn to hypermethylation.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 12-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A method comprising:

a) contacting a sample with the oligonucleotide primer which anneals and amplifies the region of the p16 gene consisting of exon 1 and a primer which anneals and amplifies the region of the p16 gene consisting of exon 2 under conditions for primer extension and producing an amplified product

b) contacting the amplified product with the primer which binds to and extends the 5' ALT gene

c) detecting the presence of a amplification production containing the amplified portions of exon 1 and 2 or detecting the presence of the amplification product of only exon 2 when the 5'ALT gene is present.

, does not reasonably provide enablement for a method of detecting methylation of a p16 gene by extension of any fragment of exon 1 and 2 wherein the absence of exon 1 is indicative of hypermethylation of 5'ALT of the p16 and the presence of a truncated product. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC.1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claim 1 is drawn to a method of detecting methylation of a p16 gene by amplification of the exon 1 and exon2 region wherein the absence of the exon 1 region wherein hypermethylation of a 5' CpG island in the first exon of the p16 gene is associated with the presence of the truncated product. Claim 13 is drawn to contacting the sample with a demethylating agent wherein the second product (exon 1) is detected

when methylation of the promoter results in truncation of the p16 gene product. Claims 14-15 define the sample. Claim 16 is drawn to a method wherein methylation of the p16 gene is indicative of a neoplasm. Claim 17 defines the neoplasm. Claim 18 define the sample. Claim 19 defines the amplification reaction.

Therefore the claims encompass a method for detecting the absence of exon 1 and the methylation of exon 1 and determining if a sample has neoplasm. It is noted that the claims have been amended to detection of RNA, however, it is noted that RNA is not methylated and therefore cannot be demethylated.

Nature of the Invention

The claims encompass method for detecting any fragment of exon 1 and 2 and the association of the lack of exon1 with any neoplasm. The invention is in a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification

The specification does not provide any specific guidance as to how to predictably detect methylation in a sample population. The tables provided by the specification and the guidance in the specification indicate that in some cases methylation can not be detected by observing an absence of the entire exon 1 region in the p16 gene.

The specification asserts the prior art has shown abnormalities of p16 gene in primary tumors of certain cancers (p. 3 lines 3-5). The specification asserts in eukaryotic cells methylation of cytosine residues immediately 5' to a guanosine occurs predominantly in CG poor regions (p. 3 lines 18-19). The specification asserts discrete regions of CG dinucleotides (CpG islands) are unmethylated in normal cells and methylation of the 5' regulatory regions lead to transcriptional repression (p. 3 lines 22-23).

The specification asserts methylated cell lines express an abundant, shortened p16 transcript devoid of exon 1 coding sequence (p. 9 last paragraph). The specification asserts hypermethylation of the 5'CpG island of p16 is frequent in cell lines and primary tumors of common human neoplasms (p. 10 1st paragraph). The specification asserts DNA methylation can occur in neoplasms with homozygous deletion (breast, renal) and those not associated with loss of p16 (colon and prostate) (p. 10 1st paragraph). The specification asserts hypermethylation in the p16 promoter region is a common abnormality of p16 in human cancers (p. 10 1st paragraph).

The claims encompass primers which extend and amplify any fragment of exon 1 and 2. The specification indicates that specific primers are used to amplify a 428 bp region of the p16 gene when the p16 gene is not methylated (p. 13 paragraph 127-131). It is unpredictable that any fragment of the p16 exon 1 and 2 is correlated to methylation, because it is the detection of the absence of the entire exon 1 fragment and not the methylation sites of the exon 1 fragment to which the claims are drawn.

The specification asserts that when the 5' ALT gene is spliced into the region right before exon 2 then the product of exon is not amplified (paragraphs 135-136). Therefore the specification indicates that the specific amplification of the entire exon 1 and 2 region is affected by methylation because the 5' ALT gene splices into the sequence and therefore the two specific primers used can not amplify the exon 1 region and the exon 2 region. The claims, however, are broadly drawn to amplification of any exon 1 or 2 region, it is unpredictable that methylation and the insertion of the 5' ALT gene into the p16 gene would affect the amplification of any region of the exon 1 or 2 by any primer.

The claims are broadly drawn to further contacting the sample with a demethylating agent. The claims are drawn to detecting the second product in the presence of the demethylating agent when methylation of the promoter results in truncation of the p16 gene product. As written the claims add the demethylation agent after extension of exon 1 and 2. It is unclear that the demethylation agent would have any effect on already amplified fragments of nucleic acids.

The specification discloses adding demethylating agent for three days to a sample and then detecting p16 mRNA (paragraph 193). Wherein the p16 mRNA was detected because there was no methylation. The claims, however, are drawn to contacting the sample with a demethylating agent in the same step of amplifying nucleic acid regions, which means that the agent can be added after extension. Further, the claims are drawn to detection of exon 1 (the second product) when methylation of the promoter results in truncation. The prior claim and the specification indicate that exon 1

is not detected when the p16 gene is methylated, however, Claim 13 indicates that exon 1 is present when the p16 gene is methylated.

Further, it is unclear the degree of methylation which must be in the sample in order to detect methylation by absence of exon 1. The specification discloses that in partially methylated cancer cell lines exon 1 and 2 were expressed (paragraph 193). Therefore the specification asserts that in the presence of exon 1 there is methylation of the p16 gene to some degree. Therefore the claims are drawn to any methylation whereas the specification indicates that the absence exon 1 is due to aberrant methylation.

The claims are broadly drawn to a method wherein the sample is contacted with the demethylation agent and the second amplification product is detected then the methylation of the p16 gene is indicative of any neoplasm. However, the specification does not show any p-values for this association. In Table 2, cell lines from cancers have intact p16 (assuming that intact p16 has both the full exon1 and exon 2) (p. 18). As discussed below, the art teaches that detection of methylation can be associated with aging, therefore, it is unclear if detection of any methylation is indicative of neoplasm. It is therefore unpredictable that any methylation detection is indicative of any neoplasm because the table indicates that methylation is not detected in all neoplastic tissue samples.

Working Examples

The examples provided by the specification, fail to provide guidance as to the detection of methylation using amplification of exon 1 and 2. The examples indicate that in some samples there is a lost of exon 2 associated with methylation. Further, the examples do not provide a clear guidance to determine if the detection of any loss of exon 1 is associated with any neoplasm.

Example 1 part 1: The specification asserts cells from head and neck cancer cell lines, lung cancer cell lines, pancreatic adenocarcinomas cell lines were extracted (p. 47 last paragraph).

Example 1 part 2 and 3: The specification asserts fragments of exon 1, 2, and 3 were amplified (p. 48 and 49).

Example 6: Table 1 presents 5' CpG island methylation related to allelic status and sequence analysis of the p16 in the cell lines. The p16 sequence indicates the majority of the primary human cancers have the wild-type p16 sequence (p. 61). This indicates p16 with exon 1 present (wildtype) would be observed in primary human cancers, therefore it is unpredictable to make an association of a mutant p16 gene (absent of exon 1) with cancers.

Example 7: The specification asserts sequence analysis of exon 1 and 2 of p16 in cell lines showed only one mutation in a HNSCC cell line (p. 62 2nd paragraph). The specification asserts the mutation caused exclusion of exon 2 but the line contained an unmethylated 5' CpG island since methylation and point mutation are independent modes of gene inactivation (p. 62 2nd paragraph). As such it is unpredictable that neoplasm or methylation can be associated with absence of exon 1. The example

provided by the specification indicates that same methylated samples do not amplify exon2 of the p16 gene.

Example 10: The specification asserts detecting de novo methylation of p16 in tumor cells (p. 65 last paragraph). The specification asserts 4 NSCLC show de novo methylation whereas one does not exhibit methylation (p. 66 Figure 6b). The specification asserts 7 of 25 NSCLC showed aberrant methylation of p16 whereas 21 control samples did not show detectable methylation (no p value provided) (p. 66 last paragraph). This is unpredictable because the specification fails to show a significant association of the methylation site of p16 and any tumor cell. It is unclear if 7 or 25 tumor cells would be statistically significant correlation of neoplasm to detection of methylation.

Example 11: The specification asserts Exon 1 of p16 lies in a CpG island which is unmethylated in normal tissue (p. 67 1st full paragraph). Table 2 shows inactivation of p16 in cell lines and primary tumors (p. 69). The specification asserts a correlation of methylation to cancer. There is no p value for the number of cell lines or tumors which had a methylated p16 region so it is unclear if there is a correlation. For example the 6 colon adenoma tumors tested only 1 was methylated. Therefore, it is unpredictable to correlate any tumor with methylation. Further, the specification asserts some primary colon cancers had hypermethylated p16 alleles while others had unmethylated alleles (p. 70 1st paragraph last sentence). It is unpredictable to detect ANY neoplasm by detection of methylation. The specification shows some tumor cell lines association

with increased methylation and other tumors (colon adenoma) where the association is not clear.

The unpredictability of the art and the state of the prior art

The current art teaches that methylation is not only caused by neoplasms, but that methylation can be detected in normal tissue. This indicates that detection of methylation does not indicate neoplastic tissue. The current art teaches detection of methylation is indicative of not only neoplasm but also aging of normal cells. Yates et al. (Oncogene 2006 Vol 25 p. 1984) teaches that methylation increases with age and malignancy (abstract). Yates et al. teaches that methylation was detected in urine DNA from patients with and without bladder cancer (Abstract). Yates et al. teaches aberrant methylation is not cancer specific and can be found in a normal ageing cell population (p. 1985 1st column 1st paragraph). Yates et al. teaches the overall knowledge of the molecular mechanisms of DNA methylation in health and cancer remains poor and one uncertainty is the extent of aberrant DNA methylation in nonmalignant tissue and the association between ageing and aberrant DNA methylation (p. 1985 last paragraph).

Quantity of Experimentation

The quantity of experimentation in this area would be extremely large since there is significant number of parameters that would have to be studied. To practice the invention as broadly as it is claimed, the skilled artisan would have to determine which fragments of exon 1 are amplified when there is not methylation versus the fragments

are absence when the tissue is methylated. Further the skilled artisan would have to determine a clear correlation between the presence of exon 1 and 2 and methylation. The specification indicates that in some instances exon 2 is absent in methylated tissue, whereas the claims are drawn to the absence of exon 1. The skilled artisan would have to determine the correlative association of every possible neoplasm and detection of methylation. It is noted that the claims have been amended to detection of RNA, however, it is noted that RNA is not methylated and therefore cannot be demethylated.

The skilled artisan would need to perform undue experimentation to determine which parts of the amplified p16 fragments are affected by methylation. There seems to be no clear pattern in the specification to guide the artisan to be able to correlate the absence of any part of exon 1 with methylation. The skilled artisan would need to perform undue experimentation to determine if detection of methylation by amplification of p16 gene is indicative of ANY neoplasm when the art shows that methylation is also indicative of other cellular processes such as aging.

To use the invention as presented would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he

scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

Thus the applicants have not provided sufficient guidance to enable a skilled artisan to make the claimed invention in a manner reasonably correlated with the claimed method of detecting methylation using any amplified fragment of exon 1 and 2 wherein the absence of the fragments of exon 1 is indicative of methylation. Further the specification does not provide guidance to the correlation of the detection of methylation to ANY neoplasm. The skilled artisan would have to perform undue experimentation to determine the relationship of the presence or absence of any fragment of exon 1 or 2 and methylation. The skilled artisan would have to perform undue experimentation to determine the relationship of ANY neoplasm and detection of methylation. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the negative teachings in the art, and the lack of guidance provided in the specification balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The reply traverses the rejection. A summary of the arguments in the reply and response to arguments is presented below. It is noted that many of the arguments below are drawn to detection of methylation in the CpG islands in the first exon. However, the claims do not contain any positive active process steps to detect methylation. Rather, the claims are drawn to the detection of amplification produces which lack exon 1. Examiner suggests that the applicant consider having an interview to discuss possible amendments to the claims before the response to the instant office action.

(A) The reply asserts that the specification discloses that there is a difference between p16 products that can be used to amplify amplicons from normal and neoplastic cells (p. 74th paragraph). The reply asserts that p16 in neoplastic cells lack sequence for exon 1, yet retain sequences fro exon 2 (p. 74th paragraph).

This argument has been thoroughly considered but has not been found persuasive.

The reply points to support for the detection of neoplasm by detection of the absence of exon 1 on pages 3-7, and 11-26. Upon review of the pages indicated and the entire specification, there is unpredictability in associating the lack of exon 1 to a prediction of a neoplasm. The specification does not provide guidance as to the association of neoplasm to absence of exon 1. Though there is data concerning methylation and hypermethylation, in the instant case the claims are drawn to detecting the absence of exon 1 of p16 in a sample. The specification does not predictably associate the absence of exon 1 of p16 with neoplasm detection. Further, the specification indicates that such associations between deletions in p16 and neoplasm are unpredictable because it is observed in cancer cell lines but not in tumors (p. 4 lines

1-10). The specification indicates that even though there is homozygous deletion of p16 in breast cancer cell lines, neither homozygous deletion or point mutations are observed in primary breast carcinomas (p. 4 lines 1-10).

Further, the specification discloses exon 1 can be detected in cancer tissue. Table 1 presents 5' CpG island methylation related to allelic status and sequence analysis of the p16 in the cell lines. The p16 sequence indicates the majority of the primary human cancers have the wild-type p16 sequence (p. 61). This indicates p16 with exon 1 present (wildtype) would be observed in primary human cancers, therefore it is unpredictable to make an association of a mutant p16 gene (absent of exon 1) with cancers.

(B) The reply asserts that the specification provides sequence information for both exons and the p16 gene (p. 7 4th paragraph). The reply asserts that the specification identifies where the truncated p16 is delimited due to insertion of the 5' ALT gene into exon 2 (p. 7 4th paragraph). The reply asserts that it is well within the abilities of the skilled artisan to design primers to any of the sequences and to amplify a sequence such that the primers would detect the presence or absence of a particular amplicon (p. 7 4th paragraph).

This argument has been thoroughly considered and has been found persuasive. In few of the teachings in the art and the specification, the skilled artisan would be able to design primers to amplify the exon 1, exon 2, and the 5 ALT region. Therefore the scope of enablement presented above has been amended to reflect the skill in the art.

(C) The reply asserts that it does not matter the time for adding the demethylation agent (p. 7 last paragraph and p. 8 1st paragraph).

This argument has been thoroughly considered but has not been found persuasive.

The addition of the demethylation agent is unpredictable in the pending claims for three reasons. (1) It is not known in the art that RNA can be demethylated. Therefore it is unpredictable to demethylate an RNA sample as claimed in the art. (2) The claims are drawn to detection of the absence of exon 1 in a sample. Whereas the demethylation agent Is demethylating the CpG islands of Exon 1. Therefore if exon 1 is absent from the same it is unclear if demethylation of exon 1 had any positive steps because the demethylation is acting on a region which is not detected. (3) The claims are drawn to detection, however, the only positive active steps are detection of the absence of exon 1. Therefore the issue with the demethylation agent is what effect, if any, it has on the final produce of the claimed invention. In the instant case, the demethylation agent is acting on an exon that is not detected.

(D) The reply asserts that regarding the degree of methylation this does not result in nonenablement to have some inoperative embodiments (p. 8 1st paragraph).

This argument has been thoroughly considered but has not been found persuasive.

It is reiterated that the claims as amended do not require any positive active step for detection of methylation. However, it is unpredictable that any methylation of the sample is correlated to neoplasm. Methylation of DNA is observed, as taught by Yang et al, in samples of older patients. Yates et al. (Oncogene 2006 Vol 25 p. 1984)

teaches that methylation increases with age and malignancy (abstract). Therefore the mere detection of methylation is not correlative to any neoplasm.

The reply seems to be asserting that with enough examples a generic claim to detection of any neoplasm can be asserted. This is not the case in the instant application. First, the claims do not require active steps of detection of methylation. Second the instant specification and the art teach that detection of methylation is not always correlative to neoplasm.

For example, Example 11: The specification asserts Exon 1 of p16 lies in a CpG island which is unmethylated in normal tissue (p. 67 1st full paragraph). Table 2 shows inactivation of p16 in cell lines and primary tumors (p. 69). The specification asserts a correlation of methylation to cancer. There is no p value for the number of cell lines or tumors which had a methylated p16 region so it is unclear if there is a correlation. For example the 6 colon adenoma tumors tested only 1 was methylated. Therefore, it is unpredictable to correlate any tumor with methylation. Further, the specification asserts some primary colon cancers had hypermethylated p16 alleles while others had unmethylated alleles (p. 70 1st paragraph last sentence). It is unpredictable to detect ANY neoplasm by detection of methylation.

(E) The reply asserts that it steps with regard to claims 12 and 13 are not contradictory (p. 8 2nd paragraph). The reply asserts that claim 13 uses functional language to describe that if demethylation results in the second amplification product being detectable that it is due to methylation of the 5' CpG island in the first exon where the effect of such methylation results in truncated p16 gene product lacking exon 1 (p. 8 2nd paragraph).

This argument has been thoroughly considered but has not been found persuasive.

The claims as written do not reflect the arguments presents. The claims only require the active process steps of detection of the absence of exon 1. Therefore it is unpredictable to demethylate an RNA sample and detect methylation of an exon which is absent from the sample.

(F) The reply asserts that the specification discloses that discrete regions of CpG islands are unmethylated in normal cells and methylation of the 5' regulatory regions lead to transcriptional repression (p. 8 3rd paragraph). The reply asserts that the claims as amended recite hypermethylation of the 5' CpG island in the first exon and it is this hypermethylation which is association with truncation of the p16 gene product and thus these regions are frequently associated with cell lines and primary tumors of common neoplasms (p. 8 3rd paragraph).

This argument has been thoroughly considered but has not been found persuasive.

The claims do not contain any active positive steps for the detection of methylation. Further, the specification asserts Exon 1 of p16 lies in a CpG island which is unmethylated in normal tissue (p. 67 1st full paragraph). Table 2 shows inactivation of p16 in cell lines and primary tumors (p. 69). The specification asserts a correlation of methylation to cancer. There is no p value for the number of cell lines or tumors which had a methylated p16 region so it is unclear if there is a correlation. For example the 6 colon adenoma tumors tested only 1 was methylated. Therefore, it is unpredictable to correlate any tumor with methylation. Further, the specification asserts some primary colon cancers had hypermethylated p16 alleles while others had unmethylated alleles

(p. 70 1st paragraph last sentence). Therefore the specification does not provide guidance for a correlation of methylation sites and neoplasm.

(G) The reply asserts that the claims embrace reversal of truncation by demethylation that is associated with neoplastic cells that can be detection by the method and do not embrace any neoplasms (p. 8 last full paragraph).

This argument has been thoroughly considered but has not been found persuasive.

The claims do not contain any active positive steps for the detection of methylation. Therefore steps to demethylate are not predictive because the claims are not drawn to any methylation steps.

(H) The reply asserts that there is variability, however, the present invention supplies the methodology steps to perform the invention (p. 87 last paragraph and p. 9 1st full paragraph). The reply asserts that the specification teaches through its examples methods for practicing the invention (p. 9 1st full paragraph).

This argument has been thoroughly considered but has not been found persuasive.

The specification does not provide clear guidance to practice the invention as claimed. The claims are drawn to detection of the absence of exon 1 without any steps towards detection of methylation. Therefore although the specification provides numerous examples these examples do not reflect the claimed invention.

(I) The reply asserts that with regard to unpredictability it is not necessary that every permutation within a generally operable invention be effective to obtain a generic invention (p. 9 2nd full paragraph).

This argument has been thoroughly considered but has not been found persuasive.

Though it is not necessary that every permutation within a generally operable invention be effect, there has to be predictability of success of the invention. Here, in the instant case, the applicant has not provided guidance to practice the invention as claimed. The claim is drawn to detection of methylation whereas the method steps do not provide any active positive steps to detect methylation. Therefore the claims are drawn to the detection of the absence of exon 1 which is reflected in the scope of enablement presented above.

(J) The reply asserts that with regard to the Wands factors, the sequence information for each exon of p16 was known, the sequence for 5' ALT is known, methylation determination is certainly not in the early stages of development, the skilled artisan would have the knowledge and abilities of using information in the specification to make and use the invention such as identify regions within p16 exons to design primers for amplification, design probes for southern blots, determine when to add demethylation agents, and the specification provides examples of method within a number of cell lines and tumor samples (p. 9 last paragraph and p. 10 1st paragraph). The reply asserts that the claims are enabled because the specification provides the appropriate guidance, working examples, and prediction of function (p. 10 2nd paragraph).

This argument has been thoroughly considered but has not been found persuasive.

The claims are drawn to detection of the absence of exon 1 of the p16 gene and there are no positive active steps for detection of methylation.
Further, the correlation of the detection of the absence of exon 1 to neoplasm is not predictive because the specification teaches that deletion of p16 is not predictability correlative to neoplasm. The specification indicates that even though there is homozygous deletion of p16 in breast cancer cell lines, neither homozygous deletion or point mutations are observed in primary breast carcinomas (p. 4 lines 1-10).

Further, the specification discloses exon 1 can be detected in cancer tissue. Table 1 presents 5' CpG island methylation related to allelic status and sequence analysis of the p16 in the cell lines. The p16 sequence indicates the majority of the primary human cancers have the wild-type p16 sequence (p. 61). This indicates p16 with exon 1 present (wildtype) would be observed in primary human cancers, therefore it is unpredictable to make an association of a mutant p16 gene (absent of exon 1) with cancers.

With regard to the methylation of exon 1, which is not detected in the pending claims because the pending claims are drawn to the detection of the absence of exon 1. Table 2 shows inactivation of p16 in cell lines and primary tumors (p. 69). The specification asserts a correlation of methylation to cancer. There is no p value for the number of cell lines or tumors which had a methylated p16 region so it is unclear if there is a correlation. For example the 6 colon adenoma tumors tested only 1 was methylated. Therefore, it is unpredictable to correlate any tumor with methylation. Further, the specification asserts some primary colon cancers had hypermethylated p16

alleles while others had unmethylated alleles (p. 70 1st paragraph last sentence). Therefore the specification does not provide guidance for a correlation of methylation sites and neoplasm.

Therefore the specification has not provided clear guidance to use the method as claimed.

Conclusion

10. No Claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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